REMARKS/ARGUMENTS

The 35 USC 112 Rejection

Claims 2-4 stand rejected under 35 USC 112, second paragraph, as being indefinite. These claims have been amended in the matter suggested by the Examiner, and should now be free from objection under 35 USC 112. These amendments do not raise new issues that would require further consideration or search, and therefore these amendments should be entered.

The 35 USC 102(b) Rejection

Claims 1-4 and 6-8 stand rejected under 35 USC 102(b) as being anticipated by the document MILLET *et* al. (Thromb. Haem., 1999). MILLET *et al.* discloses that a low molecular weight (LMW) fucoidan of 8 kDa obtained by acid hydrolysis has antithrombotic properties along with a smaller effect on coagulation of than LMW heparin. It is demonstrated that LMW fucoidan possess *in vivo* antithrombotic effect using venous thrombosis Wessler's model.

Despite the fact that the low molecular weight fractions of fucan according to the present invention are obtained by radical depolymerization and not by acid hydrolysis, the Examiner considers that this document anticipates the method as claimed and notes that the burden is on Applicant to show a novel and unobvious difference between the claimed product and the product of the prior art.

In response to this rejection, Applicant would like to argue as follows:

Firstly, as disclosed in MILLET *et al.* the ED_{80} of the 8 kDa fucoidan obtained by acid hydrolysis is about 20 mg/kg regarding the antithrombotic activity by subcutaneous injection using Wessler's model that is a venous thrombosis model (section with sub-head antithrombotic effect on page 393).

In the same model, the ED_{80} of the fucan obtained by radical depolymerization according to the Invention is 7.4 mg/kg (page 15, lines 15-16 of the application as filed). The product of the Invention obtained by radical depolymerization is thus 3-fold more active than the 8 kDa fucoidan obtained by acid hydrolysis.

Secondly, using the active dose of 20 mg/kg, the product obtained by acid hydrolysis exhibits a slight increase in anticoagulant activity when tested *ex vivo* in rabbits of about 30% to

40% of the coagulation time depending on the test (APTT or TCT) (section with sub-head ex vivo coagulation parameters on page 393).

On the contrary, the product obtained by a radical depolymerization according to the Invention and used at the active dose of about 7.4 mg/kg does not induce any significant modification of APTT or TCT time (page 25 and 26, Tables VI et VII of the application as filed). Accordingly, the use of the product of the Invention obtained by radical depolymerization at the active dose induces a weaker hemorrhagic potential than that of the product of the prior art by virtue of its lower active dose.

Therefore, it follows from the foregoing that the 8 kDa fucoidan obtained by acid hydrolysis is different from the low molecular weight fractions of fucan obtained by radical depolymerization according to the Invention.

Thus the subject matter of claims 1-12 is novel with respect to MILLET *et al.* (Thromb. Haem., 1999).

The 35 USC 103(a) Rejection

The Examiner contends that the subject-matter of claims 1, 2 and 5-10 is obvious from the teaching of NARDELLA (WO 97/08206), combined with that of COLLIEC *et al.* (US 5,321,133) and MILLET *et al.* (Thromb. Haem., 1999). The Examiner additionally rejects claims 1-12 as obvious with respect to the teaching of NARDELLA (WO 97/08206) combined with that of COLLIEC *et al.* (US 5,321,133), MILLET *et al.* (Thromb. Haem., 1999) and RACCHINI *et al.* (US 5,458,568), the last one being cited for the first time in the examining procedure.

NARDELLA (WO 97/08206) discloses a method for obtaining of low molecular weight sulphated polysaccharides using the free radical depolymerization of a fucan providing polysaccharide fractions with a molecular weight of 10,000 g/mol or less. Such products have been shown to exhibit higher *in vitro* anticoagulant properties than those of fucan fractions with similar molecular weight obtained by acid hydrolysis (Table V). However, this document never mentions the antithrombotic activity of these products, as recognized by the Examiner.

The subject-matter of COLLIEC *et al.* (US 5,321,133) relates to fucan fractions of between 5 and 40 kDa obtained by acid hydrolysis and useful as anticoagulants and

antithrombotics. However, the antithrombotic properties have been demonstrated using a venous thrombosis animal model and using fractions with a molecular weight of 20 ± 2 kDa (Example 5). Therefore, this document does not lead to the use of a fucan fraction of a lower molecular weight.

Finally, RACCHINI *et al.* (US 5,458,568) is related to a drug delivery device and method for delivering a drug locally and specifically to internal body tissue. The use of said device with antithrombotic drugs might in particular limit or prevent restenosis. This document never mentions the use of fucan fractions having a molecular weight less than or equal to 10 kDa, as in the Invention.

Applicant submits that the teaching of the documents cited by the Examiner does not lead one skilled in the art to use fucan fractions of molecular weight less than or equal to 10 kDa obtained by radical depolymerization for treating or preventing vascular thrombosis as claimed.

On one hand, (NARDELLA (WO 97/08206) is the only prior art related to the use of sulphated fucans with low molecular weight obtained by radical depolymerization. However, it never mentions that said sulphated fucans have any *in vivo* antithrombotic activity.

On the other hand, if such antithrombotic properties have been demonstrated for fucan fractions having a molecular weight less than or equal to 10 kDa, these fractions had been obtained using acid hydrolysis and only regarding venous thrombosis (MILLET *et al.*, COLLIEC *et al.*).

By using the free radical depolymerization process, the Inventors have surprisingly found that low molecular weight fucan fractions are highly effective against venous and arterial thrombosis while exhibiting no major hemorrhagic risk. In addition, low molecular weight fucans according to the Invention are also effective against arterial restenosis (page 7, lines 24-27 and example 2).

Accordingly, it is evident that the specific properties of low molecular weight fractions of fucan obtained by a radical depolymerization compared with those of the fractions of the prior art making them useful in the treatment or prevention of vascular thrombosis or restenosis have never been suggested and are not obvious over the prior art.

In view of the amendments to the claims and the foregoing comments, Applicant submits that the claims of this application patentably distinguish over the prior art and are in condition for

allowance. Favorable reconsideration by the Examiner and formal notification of the allowance of claims 1 - 12 as now presented are respectfully solicited.

It is not believed that extensions of time or fees for net addition of claims are required. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office at fax number (703) 872-9306 , on June 24, 2004.

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